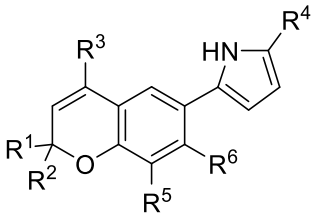
sperm production at lower doses of testosterone. However, the effects of long-term exogenous testosterone administration remain unclear. Treatment with testosterone has been associated with several negative side effects, which can include cardiac toxicity (Xu L., et al., **2013**, *BMC Medicine*, *11*, 108) and liver damage (Westaby D., et al., **1977**, *Lancet*, *310*, 261-263). The most common negative side effect was erythrocytosis, which has been linked to cerebrovascular disease (Coviello AD., et al., **2008**, *J Clin Endocrinol*, *93*, 914-919). Additionally, exogenous testosterone has been shown to lower HDL cholesterol and increase hematocrit, hemoglobin, and thromboxane, all of which are associated with cardiovascular disease (Xu L., et al., **2013**, *BMC Medicine*, *11*, 108). In addition to the more serious side effects, patients also experienced weight gain, acne, injection-site pain, and mood changes like aggression and decreased libido (World Health Organization Task Force on Methods for the Regulation of Male Fertility, **1990**, *Lancet*, *336*, 955-959). In the study described above, 2.2% of patients failed to reach the oligozoospermia threshold, indicating that certain men are "non-responders" to testosterone treatment (World Health Organization Task Force on Methods for the Regulation of Male Fertility, **1990**, *Lancet*, *336*, 955-959).

Therefore, a need exists for an effective, non-steroid hormone-based reversible male contraceptive that exhibits few if any side effects, health risks, and further complications. While hormone therapy relies on interrupting the spermatogenic process, there are far more targets for non-hormonal-based therapies that can be pursued (Blithe D., **2008**, *Contraception*, *78*, S23-S27). Non-hormonal male contraceptive approaches involve targeting proteins that affect either sperm production or sperm function and are anticipated to have minimal side effects, depending on the specificity and potency of inhibitors for the target protein.

SUMMARY

An effective, non-steroid hormone-based reversible male contraceptive that exhibits few if any side effects, health risks, or further complications has been identified. Accordingly, in one example the present disclosure provides a retinoic acid receptor-α antagonist compound of the disclosure, which is a compound of formula (I):



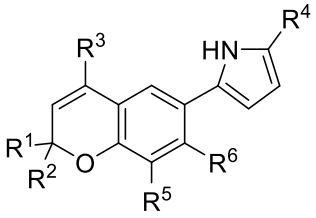
(I)

or a pharmaceutically-acceptable salt, stereoisomer, solvate, or prodrug thereof, wherein:

R^1 is H, C_1-C_3alkyl, or haloC_1-C_3alkyl;

each R^g and R^h is independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, and (C_3-C_6)cycloalkyl(C_1-C_6)alkyl; or R^g and R^h together with the nitrogen to which they are attached form an aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino ring, which ring is optionally substituted with one or more groups independently selected from C_1-C_6alkyl and haloC_1-C_6alkyl.

In an aspect, there is provided a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is C_1-C_3alkyl;

R^2 is C_1-C_3alkyl;

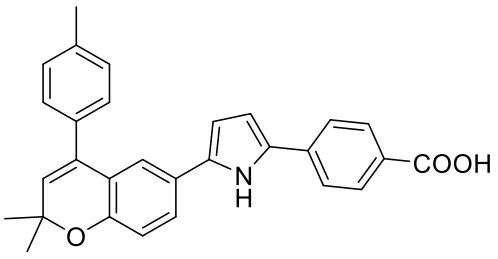
R^3 is phenyl that is optionally substituted with one or more groups independently selected from C_1-C_6alkyl that is optionally substituted with one or more groups independently selected from halo;

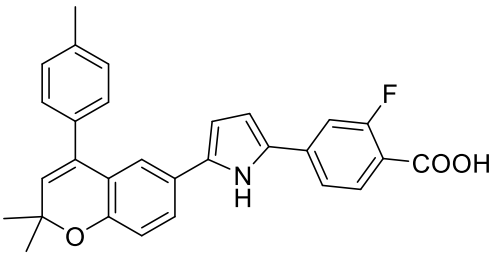
R^4 is phenyl that is substituted with carboxy and that is further optionally substituted with one or more groups independently selected from C_1-C_6alkyl that is optionally substituted with one or more groups independently selected from halo;

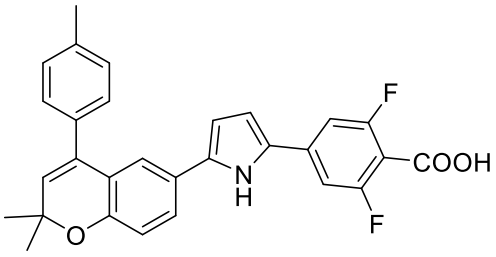
R^5 is H; and

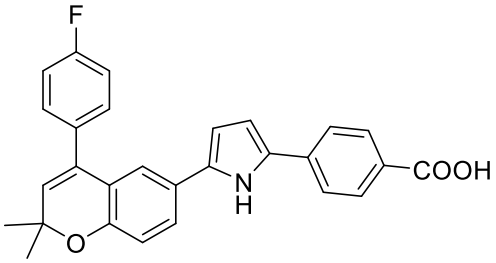
R^6 is H.

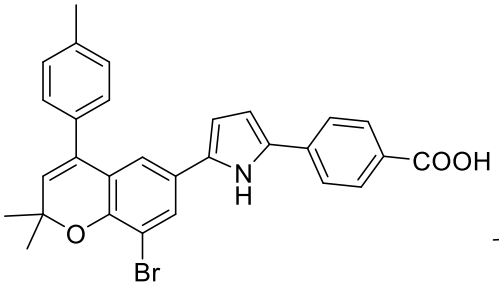
In another aspect, there is provided a compound or pharmaceutically acceptable salt that is selected from the group consisting of:

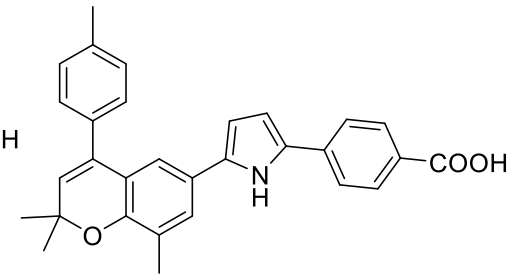


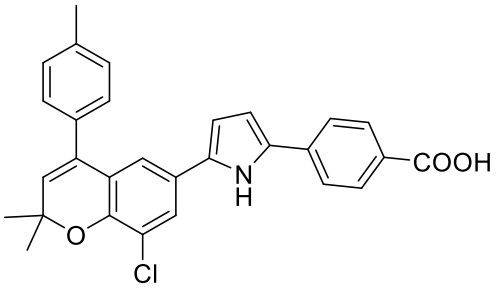


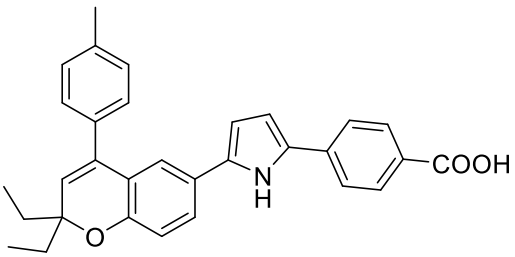

F
COOH
N
H
O
F

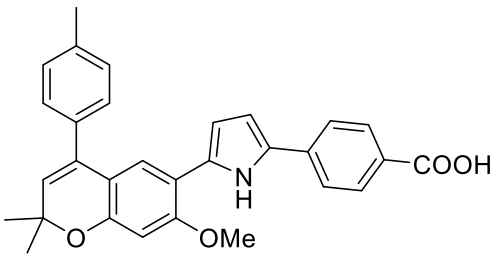

F
COOH
N
H
O

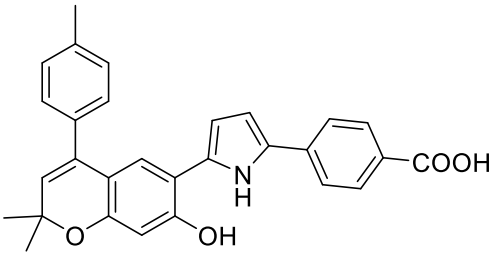

COOH
N
H
O
Br

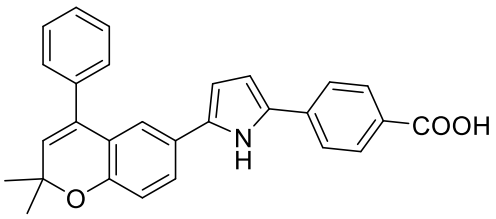

COOH
N
H
O

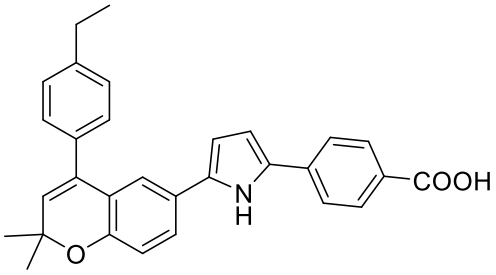

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N
H
O
Cl

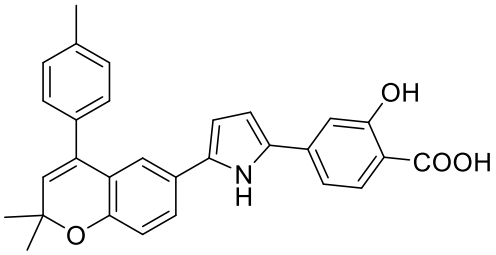

COOH
N
H
O

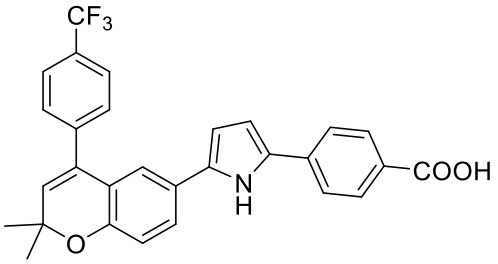

COOH
N
H
O
OMe

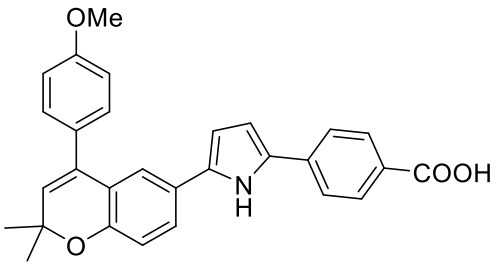

COOH
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H
O
OH

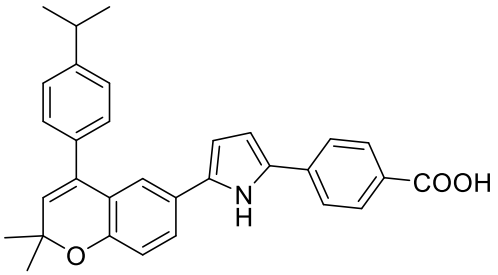

COOH
N
H
O

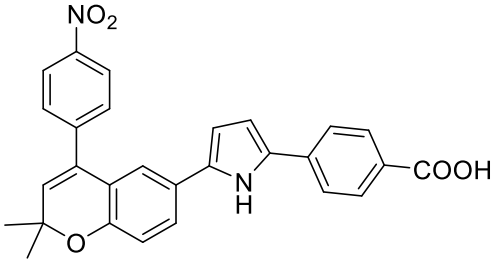

COOH
N
H
O

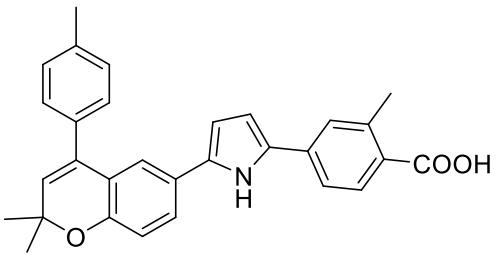

OH
COOH
N
H
O



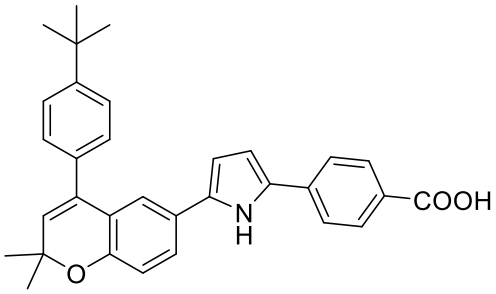








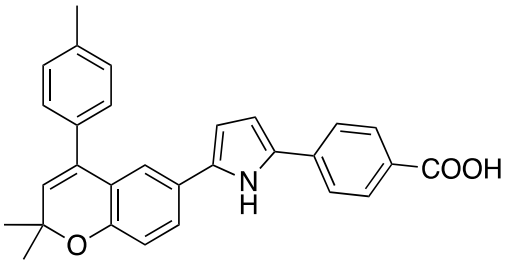
and



and pharmaceutically acceptable salts thereof.

In another aspect, there is provided a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt as defined above, and a pharmaceutically acceptable excipient.

In another aspect, there is provided a compound of the following formula:



or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a pharmaceutical composition comprising the compound as defined above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, there is provided a pharmaceutical composition comprising the pharmaceutically acceptable salt as defined above and a pharmaceutically acceptable excipient.

In another aspect, there is provided a use of a compound, as defined above, in the manufacture of a medicament to reduce sperm count in a male subject.

In another aspect, there is provided a use of a compound, as defined above, in the manufacture of a medicament to produce reversible infertility in a male subject.

In another aspect, there is provided a use of a compound, as defined above, in the manufacture of a medicament to reduce the likelihood of conception following intercourse between a male subject and a female subject, wherein the compound is to be administered to the male subject prior to the intercourse.

In another aspect, there is provided a use of a compound, as defined above, in the manufacture of a medicament for selectively antagonizing RAR alpha over RAR beta and RAR gamma in a subject.

In another aspect, there is provided a kit comprising packaging material that contains a compound as defined above and instructions for use of the compound as a contraceptive.

In another aspect, there is provided a compound, as defined above, for use in therapy.

The disclosure also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another example, the disclosure provides a method to reduce sperm count in a male subject, comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof to the male subject (e.g., a human).

In another example, the disclosure provides a method to produce reversible infertility in a male subject, comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof to the male mammal (e.g., a human).

In another example, the disclosure provides a method to reduce the likelihood of conception following intercourse between a male subject and a female subject, comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof to the male subject (e.g., a human) prior to the intercourse.

In another example, the disclosure provides a method for treating a disease or condition associated with RAR alpha activity in a subject wherein antagonism of RAR alpha is indicated, comprising administering a compound of formula (I) or a

pharmaceutically acceptable salt thereof to the mammal.

In another example, the disclosure provides a method for selectively antagonizing RAR alpha over RAR beta and RAR gamma in a subject, comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof to the subject.

In another example, the disclosure provides a method for selectively antagonizing RAR alpha over RAR beta and RAR gamma, comprising contacting RAR alpha, RAR beta, and RAR gamma *in vitro* with a compound of formula (I) or a salt thereof.

In another example, the disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in medical therapy.

In another example, the disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt thereof to reduce sperm count in a male subject.

In another example, the disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt thereof to produce reversible infertility in a male subject.

In another example, the disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt thereof to reduce the likelihood of conception following intercourse between a male subject and a female subject.

In another example, the disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt thereof to treating a disease or condition associated with RAR alpha activity.

In another example, the disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt thereof to selectively antagonize RAR alpha over RAR beta and RAR gamma *in vitro*.

In another example, the disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament to reduce sperm count in a male subject.

In another example, the disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament to produce reversible infertility in a male subject.

In another example, the disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament to reduce the likelihood of conception following intercourse between a male subject and a female subject.

In another example, the disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament treat a disease or condition associated with RAR alpha activity in a subject.

In another example, the disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament to selectively antagonize RAR alpha over RAR beta and RAR gamma in a subject.

In another example, the disclosure provides a kit comprising packaging material that contains a compound of formula (I) or a pharmaceutically acceptable salt thereof, and instructions for use of the compound of formula (I) or a pharmaceutically acceptable salt thereof as a contraceptive (e.g., to reduce sperm count in a male subject, to produce reversible infertility in a male subject, and/or to reduce the likelihood of conception or eliminate the likelihood of conception).

In another example, the disclosure provides a method to reduce sperm count in a male subject, comprising orally administering a compound that is a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to the male subject (e.g., a human).

In another example, the disclosure provides a method to produce reversible infertility in a male subject, comprising administering a compound that is a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to the male subject (e.g., a human).

In another example, the disclosure provides a method to reduce the likelihood of conception following intercourse between a male subject and a female subject, comprising administering a compound that is a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to the male subject (e.g., a human) prior to the intercourse.

In another example, the disclosure provides a method for treating a disease or condition associated with RAR alpha activity in a subject wherein antagonism of RAR alpha is indicated, comprising administering a compound that is a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to the subject.

In another example, the disclosure provides a compound that is orally active and a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to reduce sperm count in a male subject.

In another example, the disclosure provides a compound that is orally active and a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to produce reversible infertility in a male subject.

In another example, the disclosure provides a compound that is orally active and a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to reduce the likelihood of conception following intercourse between a male subject and a female subject.

In another example, the disclosure provides a compound that is orally active and a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to treating a disease or condition associated with RAR alpha activity.

In another example, the disclosure provides the use of a compound that is orally active and a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to prepare a medicament to reduce sperm count in a male subject.

In another example, the disclosure provides the use of a compound that is orally active and a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to prepare a medicament to produce reversible infertility in a male subject.

In another example, the disclosure provides the use of a compound that is orally active and a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to prepare a medicament to reduce the likelihood of conception following intercourse between a male subject and a female subject.

In another example, the disclosure provides the use of a compound that is orally active and a selective antagonist of RAR alpha or a pharmaceutically acceptable salt thereof to prepare a medicament treat a disease or condition associated with RAR alpha activity in a subject.

The disclosure also provides processes and intermediates disclosed herein that are useful for preparing a compound of formula (I) or a pharmaceutically-acceptable salt, stereoisomer, solvate, or prodrug thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows distribution data for the compound of Example 1 from Example 14.

Figure 2 shows an experimental scheme for testing the effect of the compound of Example 1 on male fertility (identified as GPHR-00354529) from Example 14.

Figure 3 shows that the administration of the compound of Example 1 (identified as GPHR-00354529) to male mice at 10 mg/kg for four weeks results in infertility two weeks post administration from Example 16.

Figure 4 shows that the administration of the compound of Example 1 (identified as GPHR-00354529) to male mice at 20 mg/kg for two weeks results in infertility four weeks post administration from Example 16.

Figure 5 shows that the administration of the compound of Example 1 (identified as GPHR-00354529) to male mice at 10 mg/kg for four weeks results in infertility and that fertility is recovered four to six weeks post administration from Example 16.

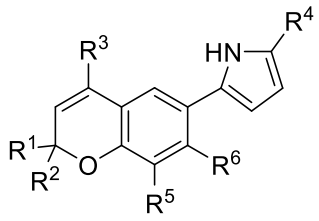
Figure 6 shows that administration of the compound of Example 1 (identified as GPHR-00354529) to male mice at 20 mg/kg for two weeks resulted in infertility and that fertility is recovered six weeks post administration from Example 16.

Figure 7 shows that 10 mg/kg of the compound of Example 1 reversibly reduces sperm counts in mice. 25 male CD-1 mice were dosed with 10 mg/kg/day (grey bars) for 4 weeks. Epididymal sperm counts were assessed once per week as of week 3 and compared to control (white bars). Shown are means±SD of absolute sperm counts from 5 mice per time point. ***$p < 0.001$, ****$p < 0.0001$. See Example 19.

CLAIMS

What is claimed is:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is C_1-C_3alkyl;

R^2 is C_1-C_3alkyl;

R^3 is phenyl that is optionally substituted with one or more groups independently selected from C_1-C_6alkyl that is optionally substituted with one or more groups independently selected from halo;

R^4 is phenyl that is substituted with carboxy and that is further optionally substituted with one or more groups independently selected from C_1-C_6alkyl that is optionally substituted with one or more groups independently selected from halo;

R^5 is H; and

R^6 is H.

2. The compound or pharmaceutically acceptable salt of claim 1, wherein R^1 is methyl.

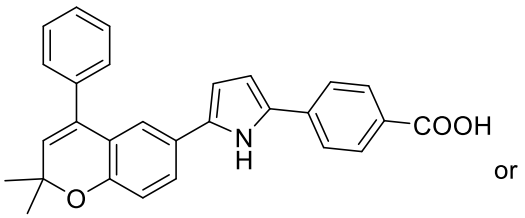
3. The compound or pharmaceutically acceptable salt of claim 1, wherein R^3 is phenyl that is substituted with C_1-C_6alkyl.

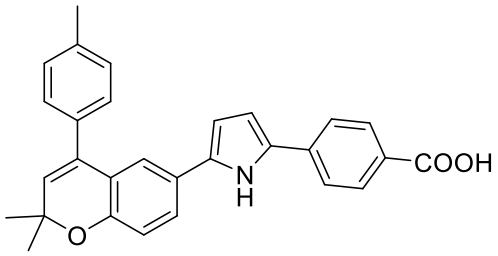
4. The compound or pharmaceutically acceptable salt of claim 1, wherein R^3 is 4-methylphenyl.

5. The compound or pharmaceutically acceptable salt of claim 1, wherein R^4 is phenyl that is substituted with carboxy.

6. The compound or pharmaceutically acceptable salt of claim 1, wherein R^4 is 4-carboxyphenyl.

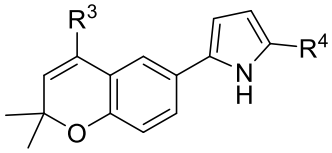
7. The compound or pharmaceutically acceptable salt of claim 1 that is:



or


or a pharmaceutically acceptable salt thereof.

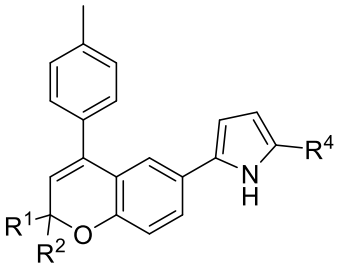
8. The compound or pharmaceutically acceptable salt of claim 1, which is a compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof.

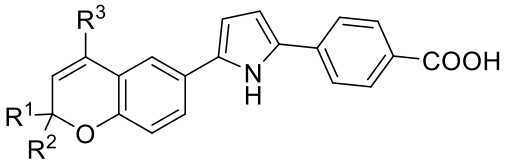
9. The compound or pharmaceutically acceptable salt of claim 1, which is a compound of formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof.

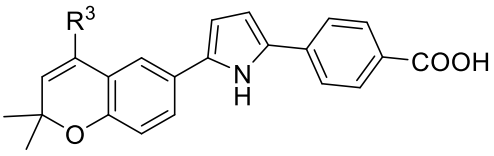
10. The compound or pharmaceutically acceptable salt of claim 1, which is a compound of formula (Ic):



(Ic)

or a pharmaceutically acceptable salt thereof.

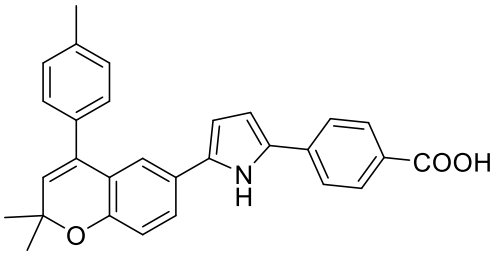
11. The compound or pharmaceutically acceptable salt of claim 1, which is a compound of formula (Id):

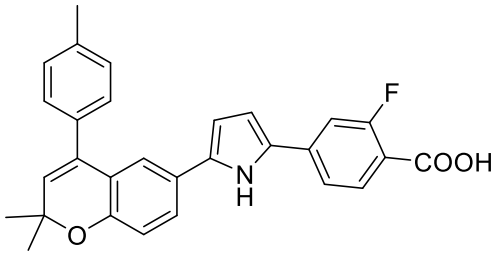


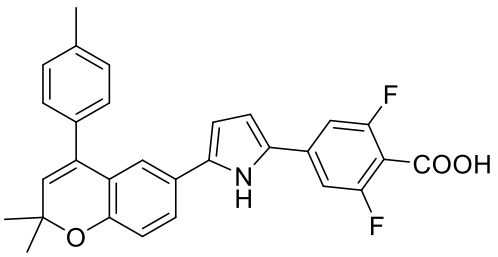
(Id)

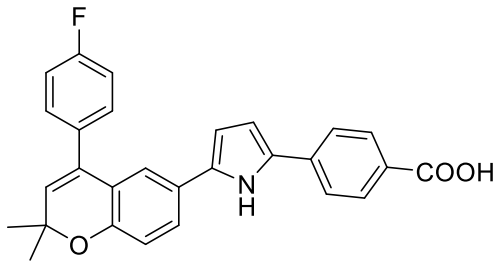
or a pharmaceutically acceptable salt thereof.

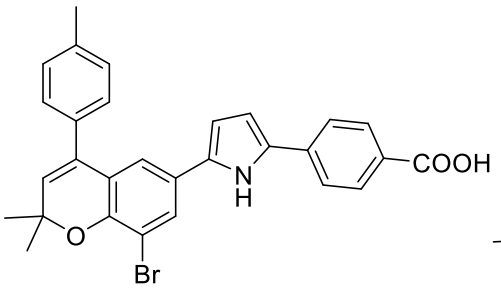
12. A compound or pharmaceutically acceptable salt that is selected from the group consisting of:

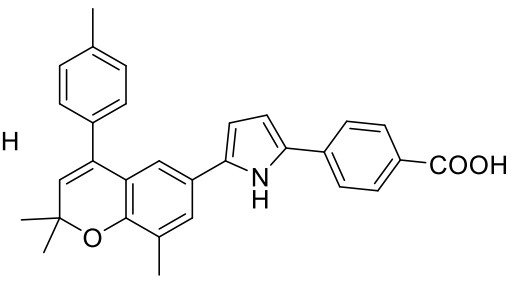


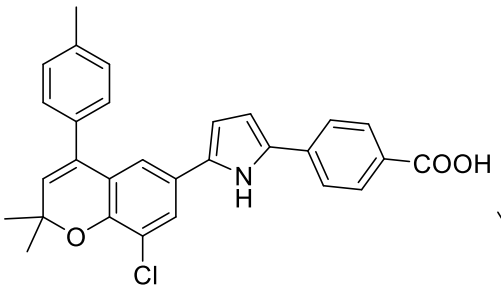


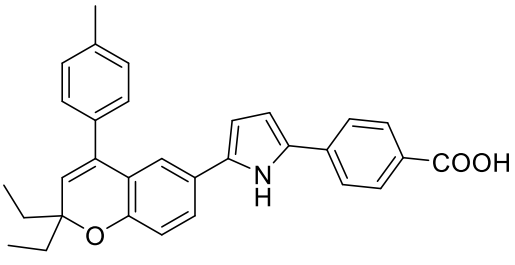


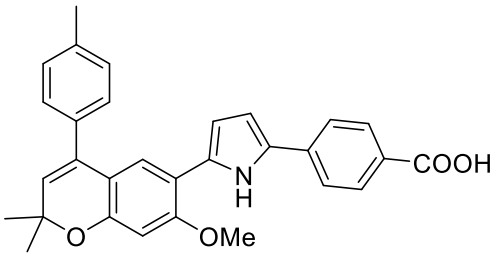


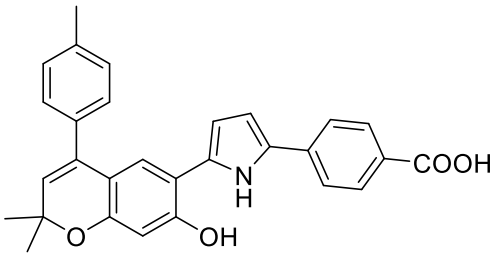


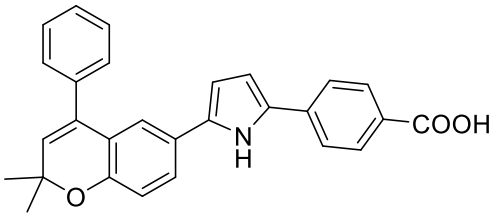


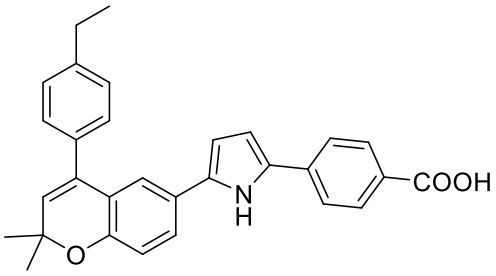


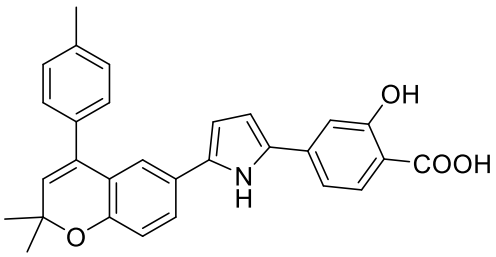


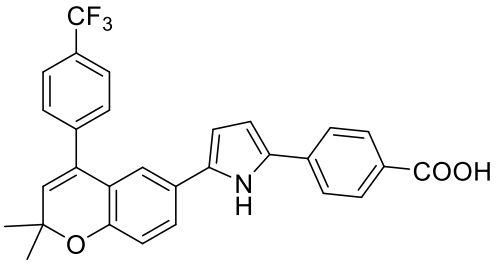

COOH
N
H
O
OMe

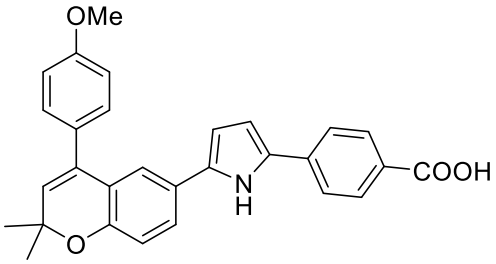

COOH
N
H
O
OH

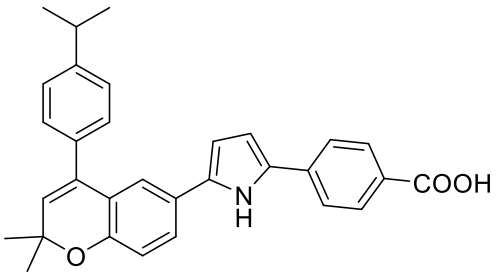

COOH
N
H
O

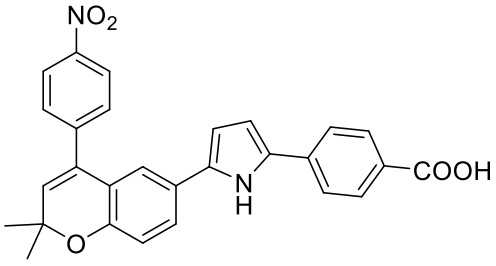

COOH
N
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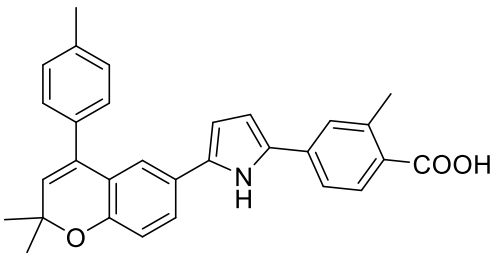

OH
COOH
N
H
O


CF3
COOH
N
H
O

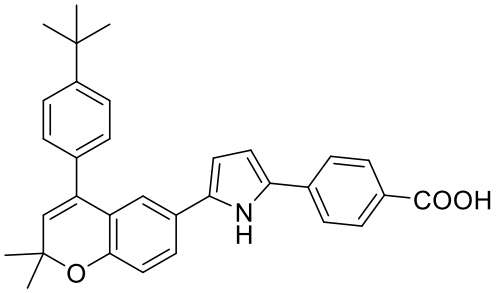

OMe
COOH
N
H
O


COOH
N
H
O


NO2
COOH
N
H
O


COOH
N
H
O

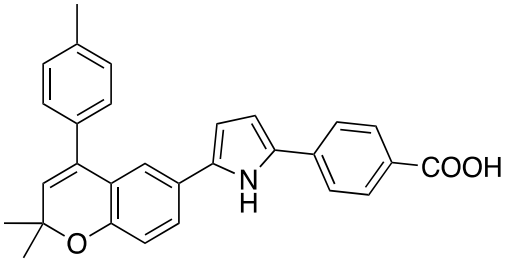
and


COOH
N
H
O

and pharmaceutically acceptable salts thereof.

13. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt as described in claim 1, and a pharmaceutically acceptable excipient.

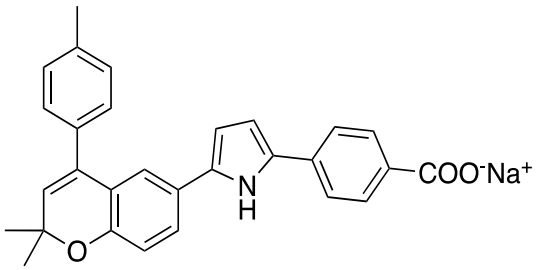
14. A compound of the following formula:



or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising the compound as described in claim 14 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

16. The pharmaceutically acceptable salt of claim 14, which is:



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17. A pharmaceutical composition comprising the pharmaceutically acceptable salt as described in claim 16 and a pharmaceutically acceptable excipient.

18. Use of a compound, as described in any one of claims 1-17, in the manufacture of a medicament to reduce sperm count in a male subject.

19. Use of a compound, as described in any one of claims 1-17, in the manufacture of a medicament to produce reversible infertility in a male subject.

20. Use of a compound, as described in any one of claims 1-17, in the manufacture of a

medicament to reduce the likelihood of conception following intercourse between a male subject and a female subject, wherein the compound is to be administered to the male subject prior to the intercourse.

21. Use of a compound, as described in any one of claims 1-17, in the manufacture of a medicament for selectively antagonizing RAR alpha over RAR beta and RAR gamma in a subject.

22. A kit comprising packaging material that contains a compound as described in any one of claims 1-17 and instructions for use of the compound as a contraceptive.

23. A compound, as described in any one of claims 1-17, for use in therapy.